18. (Unchanged) The method of claim 17 wherein biologically active portion of MBP comprises the region between amino acids 5 and 20.

Cancel claim 19 without prejudice or disclaimer.

20. (Twice Amended) A method of treating a T cell-mediated or T cell-dependent autoimmune disease in a human comprising orally or enterally administering to said human at least one member selected from the group consisting of autoantigens specific for said autoimmune disease, and autoimmune response-suppressive fragments of said autoantigens, in an amount effective to treat said autoimmune disease.

REMARKS

This is in response to the Office Action of November 9, 1992. Claims 1, 2, 9, 11-13, 15-18 and 20 are under consideration in the present application. Reconsideration is respectfully requested.

Claim 15 has been amended for greater clarity as required by the Examiner. This amendment is supported by the definition of "biological activity" on page 6, lines 20-24. Claim 19 has been cancelled. Minor and obvious amendments were made to other claims. Thus, entry of this amendment is respectfully requested as it does not add new matter to the application.

The 35 U.S.C. § 101 Rejection

Claims 1, 2, 9, 11-13, 15-19 and 20 have been rejected on the grounds of absence of patentable utility and inoperativeness. In a question of utility, 37 C.F.R. 1.132 states

> "[w]hen any claim ...is rejected...because the alleged invention is held to be inoperative or lacking in utility...affidavits or declarations traversing these...objections may be received."

Accordingly, the declaration of Dr. Weiner is enclosed for consideration. This declaration contains data from a double-blind study of oral tolerization treatment of patients afflicted with multiple sclerosis (MS) using myelin antigens.

As reported in the declaration, patients treated with myelin had fewer major attacks during the course of treatment when compared to those treated with a placebo. Further, subsets of the treated patients (namely, males and those who did not carry the HLA-DR2 phenotype) had not only fewer attacks but also achieved significant improvement as measured by the extended disability status scale (EDSS), a standard measurement of disease progression based on neurological examination. These groups also had improved physician impression and less dependence on steroidal treatment.

This trial was conducted using a protocol generally taught by the present specification and directly derived from animal studies reported in the specification. For example, the dosages were determined through empirical extrapolation of those used in the animal studies. Because of this relationship, it is believed that these results are directly applicable to the question of utility of the claimed invention.

The Declaration thus reports results which clearly show a utility in the oral tolerization treatment for multiple sclerosis. This is supported by the results found for other autoimmune

diseases in preliminary human trials as reported in the Declaration. It is then respectfully submitted that present invention, particularly in light of the data of the Weiner declaration, meets the requirement for utility under 35 U.S.C. § 101, and this rejection should be withdrawn.

The 35 U.S.C. § 112, First Paragraph Rejection

Claims 1, 2, 9, 11-13, 15-19 and 20 have been rejected as unenabled for the same reasons advanced in the rejection under 35 U.S.C. § 101.

The data presented in the Weiner declaration is believed to overcome this rejection for the reasons presented *supra*.

The 35 U.S.C. § 112, Second Paragraph Rejection

Claims 9, 15-19 and 20 are rejected as failing to distinctly point out and claim what applicant regards as the invention. Claim 15 has been specifically amended to overcome the objection to the phrase "biologically active fragments". The remainder of the objections to these claims are respectfully traversed for the following reasons.

Claim 9 and claim 1 differ in scope because of the definition of "treatment" found in the specification. On page 6, line 6, treatment is defined to include both preventative treatment and treatment after onset of the disease. Thus, the treatment method of claim 1 includes both types of treatment, yet the method of claim 9 includes only treatment which "suppresses the symptoms of said autoimmune diseases". The treatment of claim 9 must then

occur only after the onset of the disease. Thus, these two claims cannot be considered substantial duplicates.

Claims 20 and 1 differ in scope because claim 1 has as an option in the Markush group the administration of "autoantigen", while claim 20 has as an option the administration of "autoantigens". The use of a plural broadens slightly the scope of the claim. Thus, these two claims cannot be considered substantial duplicates.

Applicants thank the Examiner for calling attention to the inadvertent misnumbering error of newly added claim 20, (formerly claim 21).

The 35 U.S.C. § 103 Rejection

Claims 1, 2, 9, 11-13, 15-19 and 20 are rejected as obvious in view of the teachings of Campbell et al. in view of Whitacre et al. and/or in view of Nagler-Anderson et al.

The Examiner has conceded that the mechanism for intravenous tolerance (disclosed by Campbell) is totally different than that of oral tolerance, yet states that the teachings of Whitacre et al. and/or Nagler-Anderson et al. overcome this deficiency by teaching oral administration of autoantigen "to protect the development of autoimmune diseases, including multiple sclerosis".

It is respectfully submitted that because of the difference in mode of administration between orally insuced and intravenously attempted tolerance, the teachings of Whitacre et al. and/or Nagler-Anderson et al. cannot be used to alter the

teachings of Campbell et al. There is no motivation to combine the disclosures of Whitacre and Nagler-Anderson on one hand with that of Campbell on the other because the references provide no basis that data concerning intravenous tolerization can be applied to oral tolerization phenomena, or that oral tolerization would be effective in humans.

There is simply no expectation that an antigen employed intravenously by Campbell (which incidentally was not effective!) would be effective when orally administered in humans. Whitacre and Nagler-Anderson do not provide this expectation for the following reasons:

A. Whitacre

(1) Whitacre administered 20 mg of MBP to rats accompanied by soybean trypsin inhibitor STI to retard proteolysis of the MBP (this is disclosed in the eventual full-scale publication of the same experiments, by the same authors, see, Bitar et al, Cell. Immunol. 112:364-370, 1988 -- copy attached, particularly the footnote on page 364). Thus, Whitacre inhibited proteolysis of MBP. Whitacre 1991 also by the same authors (see citation below -- copy also attached) states that TSI appeared essential in preventing degradation of MBP.

(2) Whitacre states that oral administration of MBP "induces a state of antigen-specific unresponsiveness which could be of value in establishing therapeutic protocols for multiple sclerosis". [emphasis added] Antigen-specific unresponsiveness is also called anergy and is a different mechanism of tolerance

induction from "active suppression" which involves elicitation of antigen-specific T-suppressor cells.

(3) Whitacre states that lymphocytes or spleen cells could not transfer EAE (i.e. could not transfer disease) to naive rats. Another later publication by Whitacre et al., J. Immunol. 147:2155-2163, 1991 (copy attached) states that Whitacre was not able to transfer protection (i.e. tolerance) "adoptively" to naive rats by transferring lymphocytes or spleen cells from protected animals to naive animals prior to challenge of the naive animals. This led Whitacre to conclude that what is induced in her experiments is a state of antigen-specific unresponsiveness, or anergy, as opposed to elicitation of T-suppressor cells.

(4) Bitar states that the minimum effective amount for rats was 10-20 mg and that 1-5 mg was ineffective. By contrast, the present inventors have found in connection with several diseases that smaller amounts were even more effective than larger amounts. This serves as yet another illustration of the difference in mechanism.

(5) Whitacre was working with induced disease (as were the present inventors initially). However, unlike those of the present invention, Whitacre's findings cannot be extrapolated to humans with any expectation of success, as will be discussed further below, especially in view of the fact that (i) Whitacre's MBP was protected against degradation; (ii) Whitacre's tolerance could not be transferred; and (iii) Whitacre's attribution of her

results to anergy not active suppression (i.e. not elicitation of T-suppressor cells).

Unlike Whitacre, the present inventors who allowed MBP to be degraded in the gut, were able to elicit active suppression. See specification Example 6.

Since active suppression had been implicated in induction of tolerance to food, the present inventors were able to reason that their oral tolerization treatment worked the same way. Unlike anergy, for which the mode of action was unknown especially at the time the present application was filed, active suppression depends on events common to rodent and human immune systems. Hence, the results of the present invention could be extrapolated to humans by the present inventors. Whitacre could not do this. This is why she was forced to speculate and state only that her results "could be of value... [in] multiple sclerosis".

Anergy, the mechanism which Whitacre invokes, is not well-understood, and was not well-understood at the time of the Whitacre publication. Thus, Whitacre (or any one skilled in the art reading her papers) would not be able to expect that the regime proposed by Whitacre would work in humans. Whitacre's regime worked only to prevent induction of EAE, a condition induced by the same substance, MBP, that Whitacre then used to suppress it. Her proposed mechanism would at most allow extrapolation to a human condition induced by the same antigen. Yet, at the relevant time, there was serious disagreement as to whether MBP was responsible for causing multiple sclerosis. Thus, unlike the present

inventors, she teaches nothing about induction of tolerance orally after the subject to be treated developed autoimmune disease, and particularly after the subject develops a human autoimmune condition of unknown etiology.

Finally, degradation of antigens is necessary to induce active suppression (i.e. elicitation of T-suppressor cells). See, e.g. Zhang et al., PNAS 88:10252-56, 1991 and Michael, J.G., Immunol. Invest. 18:1049-54, 1989 (copies attached). By protecting her MBP against degradation, Whitacre was unable to induce active suppression.

B. Nagler-Anderson

The teachings of this article also suffer from the same disadvantages as Whitacre's. Again, Nagler-Anderson provides no basis why the results it describes could be extrapolated to humans. Nagler-Anderson was not capable of adoptively transferring protection, was not capable of invoking a mechanism that would permit extrapolation to humans and was by its own admission not capable of suppressing disease after its induction. In fact, Nagler-Anderson teaches away from oral treatment after the onset of disease.

For all these reasons, the teachings of Whitacre and Nagler-Anderson do not suggest that oral administration of autoantigens would work in humans.

In addition, Whitacre and Nagler-Anderson cannot be combined with Campbell to render the present invention expectable or obvious. Campbell's regime did not work (there has been no

follow up and his disclosure does not call the therapy effective) and is limited to intravenous administration. Even Whitacre's putative mechanism, anergy, does not serve to establish the propriety of the combination with Campbell. There was no evidence, reason, or expectation that anergy through the oral route would work in humans.

Additionally, it is believed that the data presented above in the Weiner Declaration is indicative of unexpected results in regards to the use of this treatment method in humans. In three different trials involving three different autoimmune conditions (multiple sclerosis, uveoretinitis, and rheumatoid arthritis) consucted in three different institutions, this treatment method has been shown to have a significant beneficial effect on the progress of the disease. It could not have been known, prior to the work in animal models as disclosed in the present invention (coupled with the postulation of a mechanism that would be likely to work in humans) that these treatments would be effective when applied to humans.

Therefore, based on the lack of motivation to combine the references, as well as the unexpected results presented in the Declaration, it is respectfully submitted that the present invention cannot be considered obvious and the rejection should be withdrawn.

Rejection under 35 U.S.C. § 102(b)/103

Claim 19 was rejected as anticipated, or alternatively obvious, over Eylar. Claim 19 has been cancelled without prejudice or disclaimer, to simplify the issues.

Obviousness-type Double Patenting

Claims 1, 9, 11-12 are provisionally rejected for obviousness-type double patenting over claims 1, 4, 9, and 17-18 of copending application Serial No. 07/596,936.

It is believed by Applicants that such a rejection is premature as the claims of neither application are in condition for allowance. When indication is made that one or the other set of claims is in such condition, the appropriate terminal disclaimer will be timely filed, and any identical claims will be cancelled from this or from the copending application.

The Rejection under 35 U.S.C. § 112, First and Second Paragraphs

Claims 1, 4-10, 12 and 15-18 are rejected for the use of the terms "autoantigen", "suppressive fragment", "immunosuppressive portion", "active fragment", and "analog". These terms are considered vague because they do not identify the kind of auto-antigen, suppressive fragment, immunosuppressive portion, active fragment, or analog. All terms are also considered too broad for the enabling disclosure.

Applicants would like to direct the Examiner's attention to the definition of "autoantigen" on page 10 of the specification. The kind of autoantigen which is to then be encompassed by the claims is any substance normally found in a mammal which is now

being abnormally attacked by the mammal's immune system, specifically for T-cell mediated or T-cell dependent autoimmune disease by the T-cells of the mammal. Even if the exact autoantigen for all autoimmune diseases have not been identified, this does not render the term vague. One of ordinary skill in the art would have no problem identifying whether a substance is an autoantigen or not, based on well known tests for measuring immune reactivity to a particular substance. If a reactivity is measured to a substance which is normally found in an animal, then that substance can be considered an autoantigen.

As to whether this term is too broad, it is respectfully submitted that the specification exemplifies two particular autoimmune diseases. Applicants need not exemplify all autoantigens for use in the present example to support the general use of the oral tolerization principle. Two separate autoimmune diseases in two disparate body systems, one nervous and one connective, have responded favorably to oral tolerization treatment. A generalized utility of this treatment method towards autoimmune diseases have been shown by the data of the specification. Therefore, generalized language, that is, the term "autoantigen", as opposed to specific recitation of the substance, is supported by the data of the specification. The clinical data for three autoimmune diseases further support this. See Weiner declaration.

The term "suppressive fragment" is simply a more descriptive term for "biologically active fragments" originally used in the specification. As can be seen by reference to the

specification, page 10, lines 19-25, the biological activity claimed for these fragments is the ability to suppress or eliminate T-cell mediated or T-cell dependent response on oral administration. It is conceded that all suppressive fragments for all autoantigens have not been identified, yet this does not render the term vague. One of ordinary skill in the art would have no problem identifying whether a fragment of an antigen is suppressive for a particular autoimmune disease or not, based on the experimental protocols presented in the Examples of the specification (e.g. overlapping peptide method).

As to whether this term is too broad, the specification supports the general term by disclosing methods of testing fragments of antigens for the ability to suppress. It is well within one of ordinary skill to use known peptide synthesis methods to construct overlapping peptide fragment sets of the antigen to be tested. These sets are then tested following the experimental guidelines of the specification, specifically Example 16. Of course, some adaption must be made for the particular animal model being used, however, such adaption is seen to not require undue experimentation. The specification supports the general principle that particular fragments of autoantigens will suppress autoimmune reactions when administered orally. Thus, general language as to fragments which suppress, as opposed to recitation of the specific fragments, is supported by the disclosure of the present application.

Based on the amendments and arguments presented above, it is respectfully submitted that the present claims are in condition for allowance. A notice to this effect is earnestly requested.

Respectfully submitted,

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Encls: Bitar et al., Cell. Immunol. 112:364-370, 1988
Whitacre et al., J. Immunol. 147:2155-2163, 1991
Zhang et al., PNAS 88:10252-56, 1991
Michael, J.G., Immunol. Invest. 18:1049-54, 1989

Declaration of Dr. Weiner and respective Exhibits

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